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Application of Organ Clearance to Estimation of the In Vivo Hepatic Extraction Ratio

Application of Organ Clearance to Estimation of the In Vivo Hepatic Extraction Ratio

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Running Title: In Vivo Estimation of Hepatic Extraction Ratio

Abstract: Organ clearance, which has been derived from the organ blood flow and extraction ratio (*E*), has been extensively used by clinical pharmacologists to explain the pharmacokinetics of many drugs in health and disease. For example, the extent of hepatic clearance or *E* (E_h) of drugs would determine their response to changes in the liver blood flow and/or activities of the metabolizing enzymes. Although E_h may be obtained directly by cannulating internal blood vessels, the method is invasive. Therefore, indirect methods have been used to estimate E_h from the peripheral blood concentration-time data after intravascular administration of drugs. Additionally, these indirect methods require an estimate of the liver blood flow in the patients or animals. However, some investigators use *plasma* concentrations and/or liver *plasma* flow for the estimation of E_h, which could potentially result in significant errors. It is shown here that when *plasma* concentrations are used along with liver *blood* flow, an overestimation or underestimation of the true value will result if the blood: plasma concentration (B:P) ratio is >1 or < 1, respectively, with the estimated E_h being different from the true value by a factor equal to the B:P ratio. On the other hand, the use of *plasma* concentrations and *plasma* liver flow will always result in an overestimation of the true E_h unless the drug does not penetrate the red blood cells. It is concluded that for the accurate estimation of E_h from the in vivo data, the *blood* concentration and *blood* flow should be used.

Key Words: Systemic clearance, organ clearance, hepatic clearance, renal clearance, hepatic extraction ratio, hepatic availability, liver blood flow, blood: plasma ratio.

INTRODUCTION AND THEORETICAL BACKGROUND

The two major organs of elimination are kidneys (excretion of unchanged drugs and/or their metabolites) and liver (metabolism and biliary excretion of drug). There are some drugs, which are almost entirely eliminated by either renal excretion of the parent drug (such as atenolol) or by hepatic metabolism only (such as propranolol) [1]. However, most drugs are eliminated by a combination of both pathways. For example, 60% of digoxin or 70% of procainamide is excreted unchanged in urine, while the remainder is metabolized by the liver [1]. The clearance (*Cl*) value obtained from the blood concentration-time data, which is sometimes called total or systemic clearance, is a summation of the individual organ clearance values contributing to the overall elimination of the drug as demonstrated in Equation (1):

$$Cl = Cl_r + Cl_h + Cl_o \quad (1)$$

where Cl_r, Cl_h, and Cl_o refer to the renal, hepatic, and other organ clearances, respectively. Among the clearance terms in Equation (1), only *Cl* and Cl_r could be directly estimated using the following equations:

$$Cl = \frac{Dose}{AUC_{0-\infty}} \quad (2)$$

$$Cl_r = \frac{A_u^{\infty}}{AUC_{0-\infty}} \quad (3)$$

where $AUC_{0-\infty}$ and A_u^{∞} are the area under the blood concentration-time curve and the amount of drug excreted unchanged into the urine from time zero to infinity, respectively. In contrast to *Cl* and Cl_r, Cl_h cannot be directly quantified in most cases. Additionally, Cl_o is unknown for most drugs. Therefore, in most literature, Cl_h and Cl_o are lumped together and presented as non-renal clearance (Cl_{nr}):

$$Cl = Cl_r + Cl_{nr} \quad (4)$$

The concept that the systemic (total) clearance is a summation of the individual organ clearances is called clearance additivity and is a useful concept for the estimation of Cl_{nr} or Cl_h indirectly once the Cl and Cl_r values are estimated directly:

$$Cl_{nr}(or\ Cl_h) = Cl - Cl_r \quad (5)$$

The concept of clearance additivity is only true when organs of elimination receive their blood supplies in parallel, such as kidneys and the liver. However, when the organs of elimination receive their blood supplies in series, such as pulmonary clearance in relationship to renal and/or hepatic clearance, the equations describing the relationship between the total and organ clearances are much more complex [2].

Loss of Drug Across an Organ of Elimination: Extraction Ratio

Figure **(1)** depicts the events that occur during the passage of a drug through an eliminating organ, such as the liver. As demonstrated, the drug enters the organ via the organ blood flow of Q and an inlet drug concentration of C_{in}. If the drug is extracted by the organ as the blood travels through it, the concentration of the drug in the blood leaving the organ (C_{out}) would be less than C_{in}. The fraction of the drug that is extracted by the liver (converted to metabolites and/or excreted into the bile) during one passage through the liver is called hepatic extraction ratio (E_h). In practice, one normally cannot directly measure what is extracted. However, E_h may be obtained from the differences in the C_{in} and C_{out} using the following equation:

$$E_h = \frac{C_{in} - C_{out}}{C_{in}} \quad (6)$$

In contrast to E_h, hepatic availability (F_h) is the fraction of the drug that escapes metabolism in the liver and is defined by Equation (7):

$$F_h = 1 - E_h \quad (7)$$

If we consider the liver as the organ of elimination, some drugs may not be eliminated (or extracted) by the liver. For these drugs, hepatic E is zero (such as drugs that are entirely eliminated by renal excretion). At the other extreme, almost all drug molecules present in the inlet blood may be extracted in one passage through the liver. For these drugs, the hepatic E is close to 1. Although a number of drugs (such as propranolol, lidocaine and propoxyphene) have high E, there is no such a drug with an absolute E_h of 1. Additionally, E_h should not be confused with the fraction of the drug metabolized by the liver (f_m). These are two entirely different parameters. For instance, a drug may be eliminated by metabolism only (fraction metabolized of 1), but its E_h may be very low. This means that the drug is metabolized slowly, but eventually all drug is eliminated by this route. Examples of such drugs are warfarin and tolbutamide with E_h values of ≤ 0.01.

Loss of Drug Across an Organ of Elimination: Organ Clearance

One of the definitions of clearance is the volume of blood cleared of drug per unit of time. For hepatic clearance (Cl_h), it is the volume of blood perfusing the liver (Q_h), which is cleared of drug per unit of time. Combining this definition with the definition of E_h, which is the fraction of the drug that is extracted by the liver during one passage, it is clear that organ clearance (in this case Cl_h) is defined by the following equation:

$$Cl_h = Q_h \cdot E_h \tag{8}$$

Based on the above discussion, the minimum and maximum values possible for hepatic clearance of drugs are zero (no hepatic extraction) and Q_h (E_h of 1).

ESTIMATION OF IN VIVO HEPATIC EXTRACTION RATIO OF DRUGS

One of the most widely used applications of organ clearance in pharmacokinetics research is the estimation the hepatic *E* of drugs in humans or animals. Estimation of E_h of drugs is important because it would allow prediction of the drug behavior when the physiologic determinants of E_h or Cl_h are altered as a result of disease states, age, or drug-drug interactions.

Direct Estimation of E_h

Direct estimation of E_h requires invasive surgical procedures to insert catheters in multiple blood vessels, which also requires laparotomy. For example, Burns et al. [3] determined the E_h of indocyanine green in rats by cannulating and obtaining blood samples from the carotid artery and hepatic vein after intravenous infusion of the marker. They then used Equation (6), substituting carotid artery and hepatic vein concentrations of indocyanine green for C_{in} and C_{out}, respectively, to estimate E_h.

In a less direct experimental design, Ward et al. [4, 5] cannulated the portal and femoral veins of monkeys and estimated the E_h of a number of drugs after their intraduodenal bolus administration using the following equation:

$$E_h = \frac{AUC_{pv} - AUC_s}{AUC_{pv}} \quad (9)$$

where AUC_{pv} and AUC_s are the portal vein and systemic (femoral vein) AUC of the drug, respectively. However, Equation (9) is valid only when the elimination of the drug is primarily through the liver, following linear pharmacokinetic principles.

In a similar procedure, Kanazu et al. [6] cannulated the jugular (systemic) and portal veins of rats and determined the hepatic availability (F_h) of midazolam after the oral and intravenous administration of the drug using Equation (10):

$$F_h = \frac{AUC_{po,systemic}}{AUC_{iv,systemic}} \times \frac{AUC_{iv,portal}}{AUC_{po,portal}} \quad (10)$$

where $AUC_{po,systemic}$ and $AUC_{iv,systemic}$ are the systemic (jugular vein) AUCs and $AUC_{po,portal}$ and $AUC_{iv,portal}$ are the portal AUCs after the oral and intravenous dosing, respectively. An estimate of E_h is then obtained using Equation (7). In contrast to Equation (9), estimation of E_h via Equation (10) does not require an assumption of hepatic elimination only.

Indirect Estimation of E_h

The E_h of drugs may be estimated indirectly from the blood concentration-time data after intravenous administration of drugs, without catheterization of the internal blood vessels, using a rearranged version of Equation (8):

$$E_h = \frac{Cl_h}{Q_h} \quad (11)$$

Generally, in these cases, the systemic clearance (Cl) of the drug is estimated from the $AUC_{0\text{-}\infty}$ data and the dose using Equation (2) ($Cl = Dose/AUC_{0-\infty}$). If the drug is almost completely eliminated by hepatic metabolism, it is assumed that Cl_h is equal to Cl, and using an average Q_h in the animal or humans, an approximate value of E_h is estimated from Equation (11). However, if the drug is subject to a measurable renal clearance (Cl_r), Cl_h is first estimated by subtracting Cl_r from Cl, using Equation (5), before substituting Cl_h in Equation (11). At best, the values of E_h obtained in this manner are approximates because other organ clearances, if indeed exist, are not normally or easily measurable without additional experimental procedures. However, in the absence of any known pathways other than Cl_h and/or Cl_r, the E_h value obtained in this manner is normally a reasonable estimate of E_h.

The Use of *Blood* versus *Plasma* (or *Serum*) Data for Indirect Estimation of E_h

It should be noted that the use of Equation (11) to estimate E_h requires the availability of *blood* (not plasma or serum) concentration-time data to be used with *blood* flow parameters. Therefore, the correct determination of E_h requires the use of hepatic blood clearance ($Cl_{h,blood}$) and blood flow ($Q_{h,blood}$) [7]:

$$E_h = \frac{Cl_{h,blood}}{Q_{h,blood}} \tag{12}$$

However, there are examples in the literature where the plasma (or serum) AUC is used interchangeably with blood AUC [8], resulting in errors in the estimation of E_h, if the blood: plasma concentration (B:P) ratio is not equal to 1. In other cases, investigators have used plasma AUCs and have divided the plasma clearance by the hepatic plasma flow [9]. As demonstrated in the following sections, both of these methods (use of *plasma* clearance and liver *blood* flow or *plasma* clearance and liver *plasma* flow) would result in substantial errors in most cases.

Errors in Indirect Estimation of E_h Using Hepatic *Plasma* Clearance and Liver *Blood* Flow (E'_h)

The hepatic extraction ratio (E'_h) obtained from the hepatic *plasma* clearance ($Cl_{h,plasma}$) and *blood* flow ($Q_{h,blood}$) is estimated using the following equation:

$$E'_h = \frac{Cl_{h,plasma}}{Q_{h,blood}} \tag{13}$$

Dividing Equation (13) by Equation (12) would result in the following relationship:

$$\frac{E'_h}{E_h} = \frac{Cl_{h,plasma}/Q_{h,blood}}{Cl_{h,blood}/Q_{h,blood}} = \frac{Cl_{h,plasma}}{Cl_{h,blood}} = \frac{f_m \cdot Dose/AUC_{plasma}}{f_m \cdot Dose/AUC_{blood}} = \frac{AUC_{blood}}{AUC_{plasma}} = B{:}P\ Ratio \tag{14}$$

where f_m is the fraction of the dose that is eliminated by the liver and B:P ratio is the blood: plasma concentration ratio. Rearranging Equation (14) would result in the following relationship between E'_h and E_h:

$$E_h' = E_h \times B{:}P\ Ratio \quad (15)$$

The relationship between E_h' and true E_h for drugs with B:P ratios of less than, equal to, or greater than 1 are shown in Figure (**2**). As shown in Equation (15) and Fig. (**2**), the E_h' value is different from the true E_h by a factor equal to B:P ratio. Therefore, whereas the value of E_h' and E_h are identical when the B:P ratio is equal to 1, when B:P ratio is > or < 1, the E_h' value is proportionally higher or lower than E_h, respectively.

Errors in Indirect Estimation of E_h Using Hepatic *Plasma* Clearance and Liver *Plasma* Flow (E_h'')

The hepatic extraction ratio (E_h'') obtained from the hepatic *plasma* clearance ($Cl_{h,plasma}$) and *plasma* flow ($Q_{h,plasma}$) is estimated using the following equation:

$$E_h'' = \frac{Cl_{h,plasma}}{Q_{h,plasma}} \quad (16)$$

The hepatic plasma flow ($Q_{h,plasma}$) is a function of hepatic blood flow ($Q_{h,blood}$) and blood hematocrit (HCT) as shown below:

$$Q_{h,plasma} = (1 - HCT) \times Q_{h,blood} \quad (17)$$

Substitution of Equation (17) into Equation (16) and rewriting the clearance terms in terms of AUC values into Equations Equation (12) for E_h and Equation (16) for E_h'' would yield Equations (18) and (19), respectively:

$$E_h = \frac{Cl_{h,blood}}{Q_{h,blood}} = \frac{f_m \cdot Dose/AUC_{blood}}{Q_{h,blood}} \quad (18)$$

$$E_h'' = \frac{Cl_{h,plasma}}{Q_{h,plasma}} = \frac{f_m \cdot Dose/AUC_{plasma}}{(1-HCT) \times Q_{h,blood}} \quad (19)$$

Dividing Equation (19) by (18) would result in the following relationships:

$$\frac{E_h''}{E_h} = \frac{\frac{f_m \cdot Dose/AUC_{plasma}}{(1-HCT) \times Q_{h,blood}}}{\frac{f_m \cdot Dose/AUC_{blood}}{Q_{h,blood}}} = \frac{AUC_{blood}}{AUC_{plasma} \times (1-HCT)} = \frac{B{:}P\ Ratio}{(1-HCT)} \quad (20)$$

$$E_h'' = \frac{B{:}P\ Ratio}{(1-HCT)} \times E_h \quad (21)$$

The relationship between E_h'' and true E_h for drugs with B:P ratios of less than, equal to, or greater than 1 are shown in Figure (**3**). Additionally, the relationship is also shown for a case when the drug does not penetrate into the red blood cells (RBC) at all (B:P ratio of 0.55, assuming a HCT value of 0.45). As demonstrated in Figure (**3**), except for the case of no RBC penetration, the value of E_h'' is always an overestimation of the true E_h, regardless of the B:P ratio. However, as expected from Equation (21), the degree of overestimation increases linearly as the B:P value increases (Fig. **3**). Only when the drug does not enter RBC at all, are the values of E_h'' and E_h identical (Fig. **3**). This conclusion may also be made from the substitution of (1-HCT) in place of B:P ratio in Equation (21) when the drug resides only in the plasma.

A comparison of Figs. (**2**) and (**3**) suggests that the use of E_h'' is potentially associated with more error than E_h'. This is because whereas E_h' is different from E_h by a factor equal to B:P ratio (Equation 15), the error in E_h'' is magnified by an additional term $[1/(1 - HCT)]$ (Equation 21).

An Example

Assume a drug was administered intravenously at a dose of 20 mg, and the plasma concentrations were used for calculation of AUC, which resulted in a values of 500 µg.h/L. Using the plasma concentrations, instead of blood concentrations, and assuming a liver blood flow of 90 L/h in a 70 kg subject and elimination by hepatic metabolism only, the E_h' of the drug is estimated to be 0.444 as demonstrated below:

$$Cl_{h,plasma} = \frac{Dose}{AUC_{plasma}} = \frac{20{,}000\ \mu g}{500\ \mu g.h/L} = 40.0\ L/h$$

$$E_h' = \frac{Cl_{h,plasma}}{Q_{h,blood}} = \frac{40.0\ \text{L/h}}{90\ \text{L/h}} = 0.444$$

If instead of hepatic blood flow, hepatic plasma flow (49.5 L/h, assuming a hematocrit of 0.45) is used, the estimated E_h'' is equal to 0.808:

$$E_h'' = \frac{Cl_{h,plasma}}{Q_{h,plasma}} = \frac{40.0\ \text{L/h}}{49.5\ \text{L/h}} = 0.808$$

As it can be seen, the values of E_h'' (0.808) and E_h' (0.444) are substantially different from each other. Now, if in reality the B:P ratio is equal to 1, E_h' would be the same as the true E_h of the drug (0.444) because blood and plasma clearances would be equal. Therefore, estimation of E_h from division of *plasma* Cl_h by hepatic *blood* flow is accurate if B:P is equal to 1. However, E_h'' (0.808) gives an incorrect answer even when the B:P ratio is equal to 1. In this case, E_h'' (0.808) would be higher than the true E_h (0.444) by factor of $1/(1 - HCT)$ or 1.82.

Now, let us assume the B:P ratio is > 1, for example 1.5. In this case, the blood AUC (AUC_{blood}) and blood Cl_h will be as calculated below:

$$AUC_{blood} = AUC_{plasma} \times B{:}P\ Ratio = 500 \times 1.5 = 750\ \mu\text{g.h/L}$$

$$Cl_{h,blood} = \frac{Dose}{AUC_{blood}} = \frac{20{,}000\ \mu\text{g}}{750\ \mu\text{g.h/L}} = 26.7\ \text{L/h}$$

Therefore, the true E_h will be 0.296:

$$E_h = \frac{26.7\ \text{L/h}}{90\ \text{L/h}} = 0.296$$

Consequently, the value of E_h' (0.444) would be an overestimation of the true E_h (0.296), by a factor equal to the B:P ratio or 1.5, when the B:P ratio is > 1. Additionally, E_h'' (0.808) would be even more overestimated because it is higher than E_h (0.296) by a factor equal to $(B{:}P\ Ratio)/(1 - HCT)$ or 2.73.

If the B:P ratio is less than 1, for example 0.7, the blood AUC (AUC_{blood}) would be 350 µg.h/L (500 x 0.7), and the blood Cl_h would be 57.1 L/h (20,000/350), resulting in a true E_h of 0.635:

$$E_h = \frac{57.1 \text{ L/h}}{90 \text{ L/h}} = 0.635$$

Therefore, E_h' (0.444) would be an underestimation of the true E (0.635), by a factor equal to B:P ratio (0.7), when the B:P ratio is < 1. Still, E_h'' (0.808) would be an overestimation of the true value of E_h (0.635), by a factor of $(B:P\ Ratio)/((1 - HCT)$ or 1.27, in the presence of B:P ratio of < 1.

Lastly, let us assume the extreme case when the drug does not penetrate into RBC at all. This is true for macromolecules such as dextrans [10] and some cell-impermeable small molecules, such as olmesartan [11]. In this case, the blood AUC would be equal to 275 µg.h/L and blood Cl_h would be equal to 72.7 L/h:

$$AUC_{blood} = (1 - Hematocrit) \times AUC_{plasma} = (1 - 0.45) \times 500 = 275 \text{ µg. h/L}$$

$$Cl_{h,blood} = \frac{Dose}{AUC_{blood}} = \frac{20{,}000 \text{ µg}}{275 \text{ µg.h/L}} = 72.7 \text{ L/h}$$

Therefore, the true E_h would be 0.808:

$$E_h = \frac{72.7 \text{ L/h}}{90 \text{ L/h}} = 0.808$$

Therefore, the true E_h is identical to E_h'' (0.808) when the drug does not enter RBC. However, as expected E_h' (0.444) is an underestimation of the true E_h (0.808) when B:P is less than 1, including this extreme case of low B:P ratio.

RECOMMENDATIONS

It is suggested that in vivo E_h should be estimated using whole *blood* concentrations and liver *blood* flow [12], whenever possible. When whole blood samples are not available and plasma samples are analyzed, the plasma data should be converted to whole blood concentrations using a separately determined B:P ratio:

$$AUC_{blood} = AUC_{plasma} \times B{:}P\ Ratio \quad (22)$$

Indeed, several investigators have correctly used this method for the estimation of E_h from the plasma data after correction for the B:P ratio [13-16]. One potential way to estimate the B:P ratio, in the absence of in vivo blood data, is by in vitro spiking of blank blood samples with the drug and measuring the total blood concentration and the resultant plasma concentrations [17]. If neither the blood concentration data nor B:P ratio is available, the use of E_h' (using *plasma* concentration and liver *blood* flow) might result in a reasonable estimate of true E_h because the B:P ratio of most drugs are close to 1. Otherwise, an overestimation or underestimation of the true value will result if the B:P ratio is >1 or < 1, respectively. The use of *plasma* clearance and *plasma* blood flow (E_h'') should be avoided because it will always result in an overestimation of the true E_h, with potentially high errors, unless the drug does not penetrate the red blood cells.

CONFLICT OF INTEREST

The author declares no conflict of interest with the content of this manuscript.

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LEGEND FOR FIGURES

Fig. (1). Graphical representations of an eliminating organ. C_{in} and C_{out} represent concentration of the drug in the blood entering and leaving the organ, respectively, and Q represents the blood flow to the organ.

Fig. (2). The relationship between hepatic extraction ratio obtained from the hepatic plasma clearance and liver blood flow (E_h') and true hepatic extraction ratio obtained from the hepatic blood clearance and liver blood flow for drugs with blood: plasma (B:P) ratios of 1.5, 1.0, and 0.7. The slope of each line is equal to the corersponding B:P ratio.

Fig. (3). The relationship between hepatic extraction ratio obtained from the hepatic plasma clearance and liver plasma flow (E_h'') and true hepatic extraction ratio obtained from the hepatic blood clearance and liver blood flow for drugs with blood: plasma (B:P) ratios of 1.5, 1.0, 0.7, and 0.55. A hematocrit (HCT) value of 0.45 is assumed in generation of these lines. The slope of each line is equal to $(B{:}\,P\ Ratio)/((1-HCT)$.

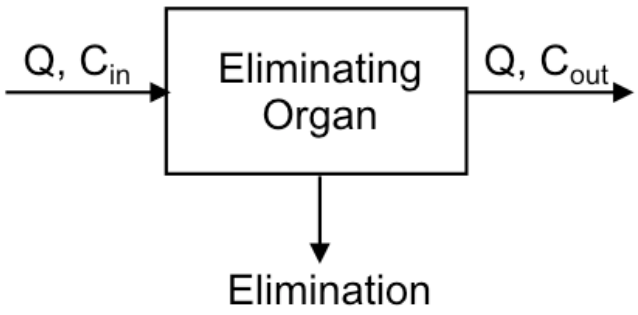

Fig. (**1**)

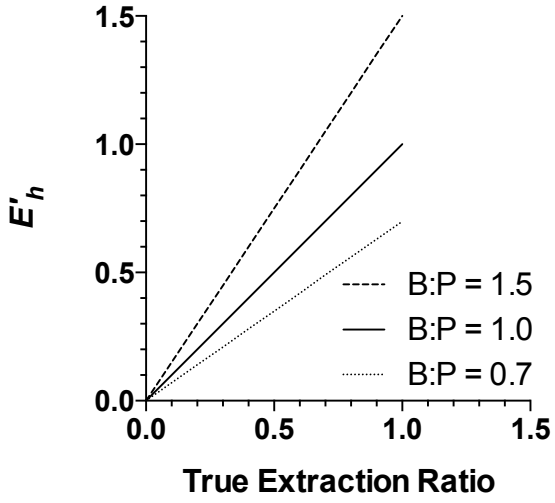

Fig. (**2**)

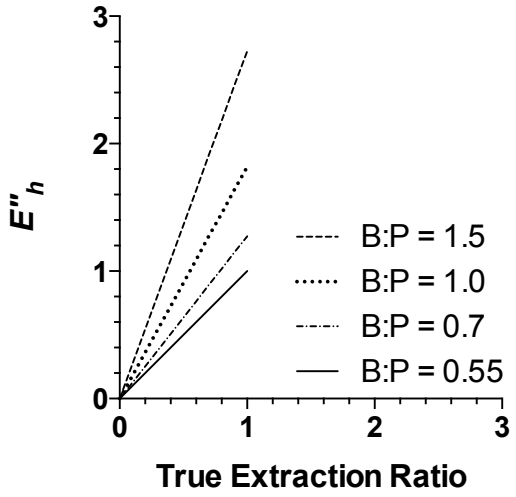

Fig. (**3**)